Letter to the Editor

New childhood and adult reference intervals for total IgE

To the Editor:

IgE plays an important role in allergy as well as in immunologic defense against parasitic infections. The measurement of serum IgE level is used in the prediction and in the diagnostic criteria for allergic disease and other immunologic disorders. The establishment of age-specific reference intervals for both children and adults is crucial because total IgE concentrations vary significantly by age. In this study, sera were collected from 1376 healthy children (702 males and 674 females) with an age range of older than 6 months to 17 years after parental permission was obtained. Patients were included on the basis of participant medical history obtained from parents, chart review (6 months to 7 years), and physical examination (7-17 years). The adults included 128 subjects (64 men and 64 women) ranging in age from 19 to 69 years. Exclusion criteria included patients taking prescription medications, with significant clinical history of a pathological condition. At the time of sample collection, none of the subjects was suffering from asthma, rhinitis, urticaria, or atopic dermatitis and none was on medications for these disorders. It is possible that some may have had seasonal allergies that were not active at the time of enrollment. Patient demographics are shown in Table I.

Total IgE concentrations were measured by using the ImmunoCAP 1000 instrument (Phadia, Uppsala, Sweden) using IgE calibrators traceable to the 2nd International Reference Preparation 75/502 of Human Serum Immunoglobulin E from the World Health Organization. Total IgE concentrations are reported in kU/L, which is equivalent to IU/mL reported in this study. Sensitivity of the ImmunoCAP system was 2 IU/mL. Testing was performed in 2 runs on consecutive days.

Data analyses were performed by using the EP Evaluator program (David G. Rhoads Associates, Inc; Release 8; Copyright 1991-2007, South Burlington, Vt). Outliers excluded from the reference interval analysis were determined as follows: Data were initially partitioned by each year of age, and outliers were eliminated on the basis of Dixon's Test or Dixon-Q Statistics. SD ratios were then calculated by using the EP Evaluator software to determine whether sex partitioning was required. Nonparametric analysis was used according to the CLSI C28-A guidelines[1] for all age groups except the 6-month to 1-year and 3-year intervals in which transformed parametric analysis was used because of n being fewer than 120.

Age-specific reference intervals were created for total serum IgE level by using data from 1376 pediatric samples (51% male, 49% female) and 128 adults (50% men, 50% women) (Table I). No significant differences were found between the following pediatric age groups, which were therefore combined: 1 and 2 years, 4 to 6 years, 7 and 8 years, 9 to 12 years, 13 to 15 years, and 16 and 17 years. It was determined that the 3-year group should remain separate. Partitioning by sex was not necessary because statistically significant (SD ratios <1.5) between-sex differences were not observed. IgE reference intervals based on these calculations are shown in Table II.

Reference intervals provided in the insert of the ImmunoCAP test system used in this study as well as other equivalent systems including the Roche MODULAR ANALYTICS E170 immunoassay analyzer were established over 35 years ago[2-5] in mostly European populations. With the incidence of allergies reportedly on the rise, the goal of this study was to establish current pediatric and adult reference intervals for total serum IgE level in a US-based population. Our reference intervals for both the pediatric and adult populations were considerably greater on the upper end than those reported previously. Compared with the Dati et al[2] study, the upper limit reported for adults was 100 IU/mL based in a German population of 99 males and 101 females. The range proposed by Zetterstrom and Johansson[4] was less than 2 to 114 IU/mL based on 175 nonatopic adults (geometric mean of 13.2 IU/mL ± 2 SD). These ranges were

TABLE I. Patient demographics for IgE reference intervals

	Pediatric		
	Total	Male	Female
Age	n	n (%)	n (%)
>6 mo, <1 y	55	39 (71)	16 (29)
1 y	73	35 (48)	38 (52)
2 y	79	30 (38)	49 (62)
3 y	81	35 (43)	46 (57)
4 y	81	48 (59)	33 (41)
5 y	79	41 (52)	38 (48)
6 y	94	53 (56)	41 (44)
7 y	62	36 (58)	26 (42)
8 y	66	32 (48)	34 (52)
9 y	58	28 (48)	30 (52)
10 y	60	26 (43)	34 (57)
11 y	85	42 (49)	43 (51)
12 y	89	48 (54)	41 (46)
13 y	80	37 (46)	43 (54)
14 y	92	47 (51)	45 (49)
15 y	90	51 (57)	39 (43)
16 y	73	36 (49)	37 (51)
17 y	79	38 (48)	41 (52)
Totals	1376	702 (51)	674 (49)

	Adult		
		Age (y)	
Sex	Total n (%)	Mean ± SD	*P* value
Male	64 (50)	35.9 ± 10.1	.8
Female	64 (50)	35.4 ± 10.6	

TABLE II. Age-specific reference intervals for total serum IgE

Age	Reference interval (IU/mL)	n
6-12 mo	2-34	52
1 and 2 y	2-97	147
3 y	2-199	77
4-6 y	2-307	247
7 and 8 y	2-403	123
9-12 y	2-696	276
13-15 y	2-629	251
16 and 17 y	2-537	144
18 y and older	2-214	121

similar to those of Dati et al[2] but still much less than the 2 to 214 IU/mL range found in our adult population. Our pediatric ranges were also much higher than those published by Dati et al.[2] Their proposed upper limit for children aged 1 to 5 years was 60 IU/mL, compared with children aged 1 to 2 years (97 IU/mL), 3 years (199 IU/mL), and 4 to 6 years (307 IU/mL) in our study (Table II). In the same study, the upper limit for children aged 6 to 9 years was 90 IU/mL and for children aged 10 to 15 years was 200 IU/mL. These ranges were again substantially less than those determined in our study (an upper limit of 403 UI/mL for children aged 7-8 years and 629 IU/mL for children aged 13-15 years). The reference intervals for the Dati et al[2] study were based on 280 children compared with 1376 children included in our study. Reference intervals cited in the ImmunoCAP System's package insert were based on 466 healthy children from 2 independent studies, both using the PRIST immunoassay system.[3,5] Reference intervals calculated from these combined studies gave an upper limit of 84 IU/mL (geometric mean ± 2 SD) for their 5-year-old group and an upper limit of 148 IU/mL for children aged 10 years. These values were again similar to the values in the Dati et al[2] study but much lower than ours, in which we had an upper limit of 307 IU/mL for children aged 4 to 6 years and 696 IU/mL for children aged 9 to 12 years.

For our pediatric sample group, total serum IgE values peaked at age 10 years and then declined to adult values. This trend is consistent with that reported by Kjellman et al[3] and Zetterstrom and Johansson[4] in their pediatric populations.

These dramatic differences between the upper limits established in our study and values published previously, but still commonly cited in current immunoassay systems, emphasize the need for updated reference intervals for total serum IgE.

The prevalence of allergic diseases is increasing globally, with about 30% to 40% of the world population affected by 1 or more allergic conditions. It has been reported that total IgE concentrations are affected by a wide variety of factors including sex, age, geographic location, and diet, as well as environmental factors and climate change.[6-12] Although none of the individuals we included demonstrated obvious allergic disease at the time we enrolled them, such factors could have a role in explaining the markedly elevated normal values for IgE we observed. We believe that these proposed reference intervals more accurately reflect values found in today's US population. This is based on the large study size of 1376 children and 128 adults, as well as using approved guidelines for establishing reference intervals in the clinical laboratory.[1] Because most current immunoassay systems for quantitating total serum IgE are calibrated against the current World Health Organization International Reference Preparation, these newly established reference intervals should be relevant to other assay systems.

Thomas B. Martins, MS[a]
Michael E. Bandhauer, BS[a]
Ashley M. Bunker, BS[a]
William L. Roberts, PhD[a,b]
Harry R. Hill, MD[a,c]

From [a]the ARUP Institute for Clinical and Experimental Pathology, [b]the Department of Pathology, University of Utah, and [c]the Departments of Pathology, Pediatrics and Medicine, University of Utah School of Medicine, Salt Lake City, Utah. E-mail: martintb@aruplab.com.

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